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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,635	09/22/2000	Kendall A. Smith	2650/1F918-US1	2206

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,635	SMITH, KENDALL A.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 15, and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/02/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Office Action

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the response filed 02 October, 2003. No claims were amended and new claims 13-16 introduced. Newly submitted claims 13 and 14 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed toward *ex vivo* delivery methods involving gene therapy protocols that require different reagents and protocols from the currently claimed procedure. Accordingly, the claims are clearly directed toward an independent and distinct invention. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 13 and 14 are withdrawn from further consideration as being directed towards a nonelected invention (refer to 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03). Claims 1-12, 15, and 16 are currently under examination.

Information Disclosure Statement

2. The information disclosure statement filed 02 October, 2003, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

3. Claims 1-12, 15, and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims reference a method for the "potentiation of an immune response to an infectious disease" which is vague and indefinite. The term "potentiation" has an art-

recognized meaning and refers to a pharmacological interaction between two or more agents/drugs that results in a pharmacologic response that is greater than the sum of the individual responses to each drug or agent.[1] However the methodology only describes the administration of a single agent (IL-2). It does not disclose the administration of another agent or describe the various effects that are potentiated by IL-2 and the other agent. The phrase referencing an amount of IL-2 that is sufficient to "maintain immune enhancement" is also vague and indefinite since the precise immunological properties affected are not disclosed. For instance, do the claims encompass increased or decreased cytokine production, increased or decreased humoral responses, increased or decreased cell-mediated responses, or some other immunological parameter? Applicants should amend the claim language to describe the invention more clearly.

4. Claim 9 is also vague and indefinite for referencing an "immune reconstituted" subject since the precise genotype/phenotype are not readily manifest. How has the subject been "reconstituted"? What immune functions have been restored? What cell populations or targets have been affected? Appropriate amendment and clarification are required.

35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

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[1] See Stedman's Medical Dictionary, 27th edition.

> matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

6. The previous rejection of claims 1-12 under 35 U.S.C. § 103(a) as being unpatentable over Lane *et al.* (2001), is hereby withdrawn in view of the new grounds of rejection set forth below.

7. Claims 1-4, 8-10, 15, and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lane *et al.* (2001) in view of Vandamme *et al.* (1998). Lane and colleagues disclose a low-dose (e.g., 1.8×10^6 U) method for the administration of interleukin-2 (IL-2) to increase immune function in a human subject, comprising administering an amount of IL-2 to a human subject in an amount that is sufficient to increase the $CD4^+$ cell count in the subject as compared with the count prior to IL-2 administration. The inventors state (see col. 5, lines 27-52) that:

> The present invention provides a method for increasing the level of immune function of patients, including immunodeficiency patients, by administering IL-2. The increase in immune function typically manifests itself as an increase in helper/inducer T-cell function. More particularly, the increased immune function can include, for example, an increase in CD4 count, a restoration of lymphocyte function, an increase in the expression of IL-2 receptors (IL-2r), and/or an increase in T-cell responsiveness.
>
> The methods of the present invention can be effective against disease states in which IL-2 plays a role in the associated immune response. The targeted disease state can comprise, for instance, an infection of the patient by a pathogen against which a cellular immune response is the principal mechanism for specific immunity therefor in the patient, such as viral infections ... Illustrative of specific disease states in treatment of which the present invention can be applied are HIV infection and other diseases

characterized by a decrease of T-cell immunity ....

The disclosure also provides various dosages (e.g., 1 MU/day to 24 MU/day [col. 7, lines 35-46) and notes (e.g., see col. 2, lines 37-51) that even lower dosages (e.g., 0.025 MU/day to 1 MU/day) were reported in the prior art. Thus, this teaching unequivocally demonstrates that IL-2 administration, in low-doses, can have a positive effect on the immune system that manifests itself in the form of increased $CD4^+$ T-lymphocyte counts, increased T-cell responsiveness, and a restoration of lymphocyte function. This teaching also clearly illustrates that IL-2 administration will benefit those suffering from viral infections, such as HIV. The only limitation of this teaching is that it does not specifically address the timing of IL-2 administration with respect to the discontinuation of viral therapy or prior to a vaccination regimen. The examples in this reference actually employed the concomitant administration of both IL-2 and an antiviral agent to HIV-1-infected patients.

Vandamme *et al.* (1998) teach that currently available antiretrovirals are associated with numerous problems, including viral resistance, drug-drug interactions and adverse side-effects. Patients frequently become noncompliant because of these problems and need alternative forms of therapy.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to administer low-dose IL-2 therapy to virally infected patients (e.g., HIV-1) as taught by Lane *et al.* (2001), after the discontinuation of antiretroviral therapy, since Vandamme *et al.* (1998) disclose that patient compliance while on antiretrovirals is problematic. Thus, one of ordinary skill in the art would have been motivated to administer low-dose IL-2 therapy to virally-infected patients since this would provide a useful means for activating and restoring immune function in patients who can no

longer tolerate antiretroviral therapy. Moreover, antiretrovirals are not directed toward the immune system and many virally infected patients suffer from immune dysfunction.

8. Claims 5-7, 11, and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tilg *et al.* (1993) in view of Tsai and Huang (1997). Tilg and colleagues (1993) disclose the administration of low-dose IL-2 therapy to HBV-infected patients who are not undergoing antiviral therapeutic regimens. The authors conclude that low-dose IL-2 was clearly biologically active. This teaching does not disclose the administration of IL-2 to HCV-infected patients. However, Tsai and Huang (1997) report that both HBV- and HCV-infected patients utilize similar immune mechanisms to remain in asymptomatic states. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to administer low-dose IL-2 therapy as taught by Tilg *et al.* (1993), to HCV-infected patients, since Tsai and Huang (1997) disclose that vigorous immune responses in both HBV- and HCV-infected patients appears to control viral replication. One of ordinary skill in the art would also have been motivated to include a known antiviral (e.g.,ribavirin) in the therapeutic regimen as well, since this would result in the direct inhibition of viral replication in conjunction with increased immune responsiveness.

Non-statutory Double Patenting

9. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re*

Vogel, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

10. Claims 1-12, 15, and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-57 of U.S. Patent No. 6,509,313 in view of Vandamme *et al.* (1998). Although the conflicting claims are not identical, they are not patentably distinct from each other. This teaching ('313) discloses the administration of low-dose rIL-2 to HIV- and HCV-infected patients to boost the immune system. While, this teaching does not discuss the timing of the administration in reference to antiviral therapies, nevertheless, Vandamme *et al.* (1998) discloses that antivirals are often toxic, lead to drug-resistant variants, and patient noncompliance. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to administer low-dose IL-2 therapy to virally infected patients (e.g., HIV-1) as taught by Smith in the '313 patent, after the discontinuation of antiretroviral therapy, since Vandamme *et al.* (1998) disclose that patient compliance while on antiretrovirals is problematic. Thus, one of ordinary skill in the art would have been motivated to administer low-dose IL-2 therapy to virally-infected patients since

this would provide a useful means for activating and restoring immune function in patients who can no longer tolerate antiretroviral therapy. Moreover, antiretrovirals are not directed toward the immune system and many virally infected patients suffer from immune dysfunction.

11. Claims 1-12, 15, and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,045,788. Although the conflicting claims are not identical, they are not patentably distinct from each other. This teaching ('788) discloses the administration of low-dose rIL-2 to HIV- and other virally-infected patients to boost the immune system. While, this teaching does not discuss the timing of the administration in reference to antiviral therapies, nevertheless, Vandamme *et al.* (1998) discloses that antivirals are often toxic, lead to drug-resistant variants, and patient noncompliance. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to administer low-dose IL-2 therapy to virally infected patients (e.g., HIV-1) as taught by Smith in the '788 patent, after the discontinuation of antiretroviral therapy, since Vandamme *et al.* (1998) disclose that patient compliance while on antiretrovirals is problematic. Thus, one of ordinary skill in the art would have been motivated to administer low-dose IL-2 therapy to virally-infected patients since this would provide a useful means for activating and restoring immune function in patients who can no longer tolerate antiretroviral therapy. Moreover, antiretrovirals are not directed toward the immune system and many virally infected patients suffer from immune dysfunction.

12. The following prior art, which was not relied upon in the

office action, is considered germane to applicant's disclosure:

- Bernstein, Z. P., *et al.*, 1995, "Prolonged administration of low-dose interleukin-2 in human immunodeficiency virus-associated malignancy results in selective expansion of innate immune effectors without significant clinical toxicity", Blood 86(9):3287-3294.

- Jacobson, E. L., *et al.*, 1996, "Rational interleukin 2 therapy for HIV positive individuals: Daily low doses enhance immune function without toxicity", Proc. Natl. Acad. Sci USA 93:10405-10410.

- Smith,K. A., 04 September, 1997, "Stimulation of immune response with low doses of interleukin-2", WO 97/31622.

- Kakumu, S., *et al.*, 1988, "Pilot study of recombinant human interleukin 2 for chronic type B hepatitis", Hepatol. 8(3):487-492.

Correspondence

13. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward the following Group 1600 fax number: (703) 872-9306. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (703) 308-1122 or (703) 308-4027, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

24 January, 2004